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TUMORS OF PERIPHERAL NERVES*

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The term neuroma was introduced into medical literature by Odier of Geneva in 1803. The term was applied by him to tumors formed by the diseased enlargements of nerves. William Wood published in the *Transactions* of the Medico-Chirurgical Society of Edinburgh, appearing in 1829, records of some twenty-four cases of neuroma which he had collected from various sources. A clear description of the anatomical and clinical features of these enlargements was given. In this paper Wood cited eight cases in which the tumor had been successfully removed. Some of these are of considerable interest. One appeared in Cheselden's "Anatomy of the Human Body," published in 1773; another in the "Encyclopédie Méthodique de Chirurgie," Paris, 1792, and in this instance an amputation was performed for what was undoubtedly a plexiform neurofibroma of the median nerve in the forearm. Another case was reported in a paper by Sir Everard Home. He describes a case in which he was assisted by John Hunter in the removal of a tumor from the musculocutaneous nerve in the arm. Another case is recorded by Sir Charles Bell, in which he removed a tumor from the internal popliteal nerve. Wood believed that these growths developed from the connective tissue of the nerves and not from nerve substance proper.

A number of articles dealing with neuromas were published during the succeeding years. Smith, of Dublin, in 1849, recognized that neuromas might be of spontaneous origin, or that they might follow division or injury of a peripheral nerve. He gave an exhaustive account of "multiple neuromata," based upon autopsy findings in two remarkable cases. He did not believe, however, that the tumors were composed of nerve tissue. He thought that they developed from the connective tissue. Sarcomas of nerves were not mentioned in these early publications.

With the introduction of new histological methods and improvements in histological technic, a new classification of neuromas appeared. Heretofore, the term neuroma had been applied rather indiscriminately to tumors of different kinds and to a number of lesions affecting nerves which were probably not tumors. The histology of nerve fibres had advanced considerably

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when Virchow, in 1863, gave a classification of these tumors based upon a structural instead of a clinical basis. He divided these tumors first into the true and false. The true neuroma was defined as a tumor which was composed for the most part of newly formed nerve tissue. The false neuroma was thought to be composed of connective tissue derived from the sheaths of the nerve. He divided true neuromas into three groups—the neuroma gangliocellulare, composed of newly formed nerve cells; the neuroma fibrillare amyelinicum, composed mostly of non-medullated nerve fibres; and the neuroma fibrillare myelinicum, composed chiefly of medullated nerve fibres. Virchow thought that many of the cases of neurofibromas were in reality true neuromas, composed of non-medullated nerve fibres. Nerve fibres might, however, easily be mistaken for connective tissue fibres, if special staining methods were not employed. He also suggested that a true neuroma might be converted into a fibroma, if pressure caused disappearance of the nerve fibres. The histological structure of these tumors revealed by the use of specific stains, indicates that many of Virchow's contentions as to the structure of these tumors can no longer be maintained.

In the Laboratory of Surgical Pathology of the Johns Hopkins Hospital are over 180 tumors which are classified as fibromyxomas or fibromyxosarcomas of peripheral nerves. About forty of these tumors were placed in the sarcoma group. The sections of the tumors were restudied. The typical benign tumors, showing in places the palisade arrangement of the nuclei and in other areas the reticular structure (to be discussed in more detail later), could be easily picked out. The tumors occurring in von Recklinghausen's disease and sarcomas arising from nerves could not be so easily distinguished. All the histories were then reviewed. In some the data were incomplete; in many there was no positive evidence that the tumor was connected with a nerve. It should be noted that the connection of the typical benign tumor with a nerve could be easily demonstrated. All the sarcomata included in this paper had a definite origin from or connection with a nerve.

Thirty-seven cases of proven peripheral nerve tumors were available for study. These are classified as follows:

Neurinomas (with palisade arrangement of the nuclei and reticular structure)	11	Von Recklinghausen's disease without tumors of deep nerves	5
Benign tumors (sections lost; diagnosis made from history and original pathological notes)	4	Von Recklinghausen's disease with deep nerve tumors, malignant 4, benign 7	11
Sarcomas	3	Localized cutaneous neurofibromatosis	1
		Tumor in neck, one showing ganglion cells	2

Benign Solitary Tumors, Neurinomas, Perineurial Fibroblastoma (fourteen solid, one cystic).—All of the solid tumors occurred in adults, the ages of the patients ranging from twenty-eight to sixty-five years, the average

being forty-four. They were equally distributed between males and females. The duration of the tumor before removal by operation in the twelve cases in which it was recorded ranged from six months to ten years, with an average duration of three and one-half years.

The distribution according to nerves is as follows:

Median	3	Cutaneous branch of posterior tibial	1
Radial	2	Branch of intercostal nerve	2
Sciatic	2	Lesser internal cutaneous	1
Posterior tibial	2	External popliteal	1
Cutaneous branch of external popliteal	1		

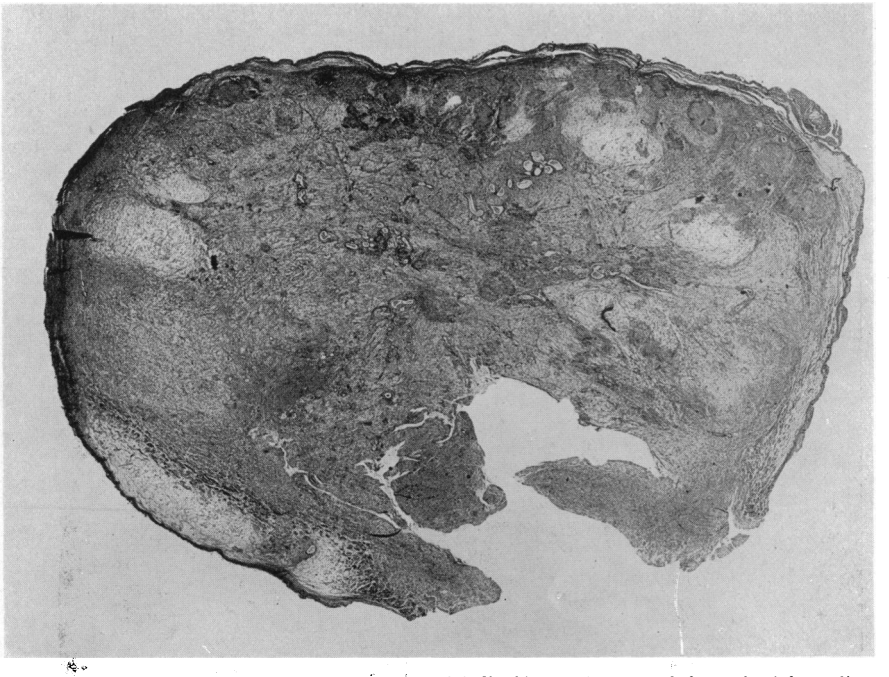

FIG. 1.—Solitary tumor (neurinoma, perineurial fibroblastoma) removed from the left median nerve in the lower part of the axilla. Capsule of tumor is broken at one point. In the middle part of the upper portion are islands of type A tissue. The greater part of the tumor is made up of type B, reticular tissue. Myxomatous changes have occurred in the tumor.

The three following histories will be cited to indicate the clinical characteristics of the benign group of tumors. These three cases are selected as they are typical.

CASE I.—Mrs. S. G., aged fifty-four years, was admitted to the Johns Hopkins Hospital, January 26, 1928. A year before admission she first noticed a shooting pain down the outer surface of the left arm. She did not pay much attention to this at first. It became more severe. Five months before admission a small, tender swelling was noted under the left arm just below the anterior axillary fold. When pressure was made upon this nodule pain radiated into the forearm and hand along the distribution of the

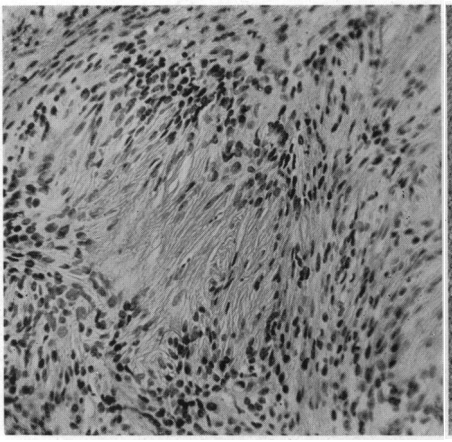

FIG. 2.—High power of a section of preceding tumor showing typical palisade arrangement of the nuclei. This arrangement is characteristic of this type of tumor of nerve trunks. It should be remembered that a similar histological picture may be found in a rapidly growing myoma.

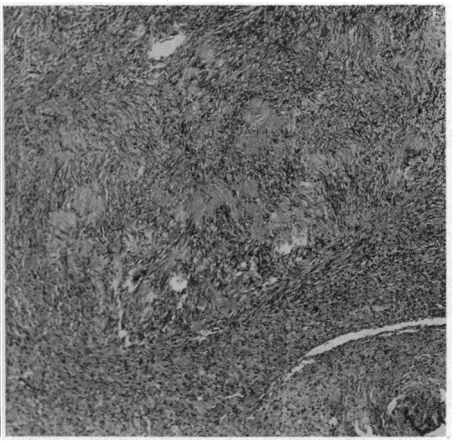

FIG. 3.—High power of a section made from a tumor arising from the dorsal root of a spinal nerve, showing the typical histological picture of type A tissue found in neurinoma (perineurial fibroblastoma).

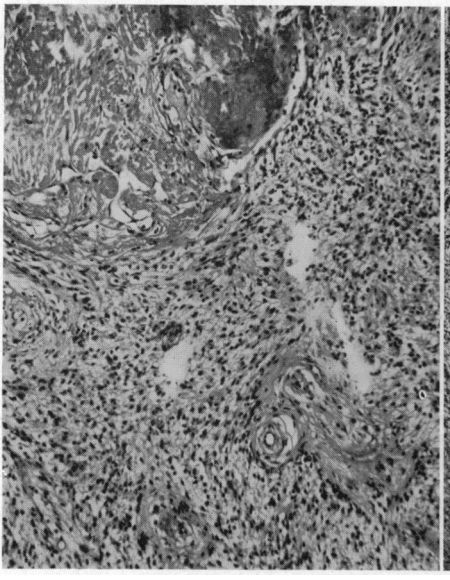

FIG. 4.—High power of a section through a solitary tumor removed from the left popliteal nerve. This tumor had a myxomatous appearance. Some funiculi were resected in removing this tumor, the major part of which could be enucleated. This tumor was composed almost entirely of type B, the loose reticular tissue, with a tendency to myxomatous changes, described by Verocay.

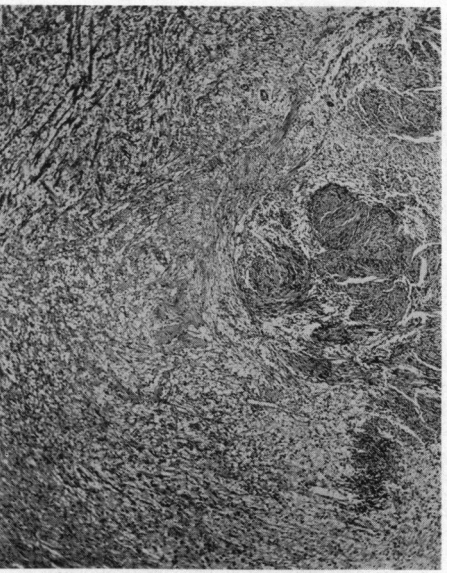

FIG. 5.—High power of a section of large tumor removed from the sciatic nerve. Resection of the nerve was necessary because several funiculi passed through the tumor. This is the only one of fifteen solitary tumors which required resection. End-to-end suture performed. No recurrence after almost two years. Considerable return of function. Whorls of type A tissue with palisade arrangement of nuclei are interspersed among reticular type B tissue.

median nerve. There has been no numbness, tingling or weakness of the parts to which the pain has radiated.

On January 27, 1928, under local anæsthesia, the trunks of the brachial plexus were exposed and the nerves blocked. A small tumor was found in the median nerve. The sheath of the nerve was split and a tumor as large as a large hazelnut was shelled out. The tumor could be removed without sacrificing any nerve fibres. The sheath of the nerve was then sutured with fine silk.

This patient has fully recovered. For a while she complained of some peculiar sensory disturbances over the course of the median nerve. These have disappeared and there have been no evidences of return of the tumor. The histology of the tumor, which grossly had a myxomatous appearance, will be discussed later.

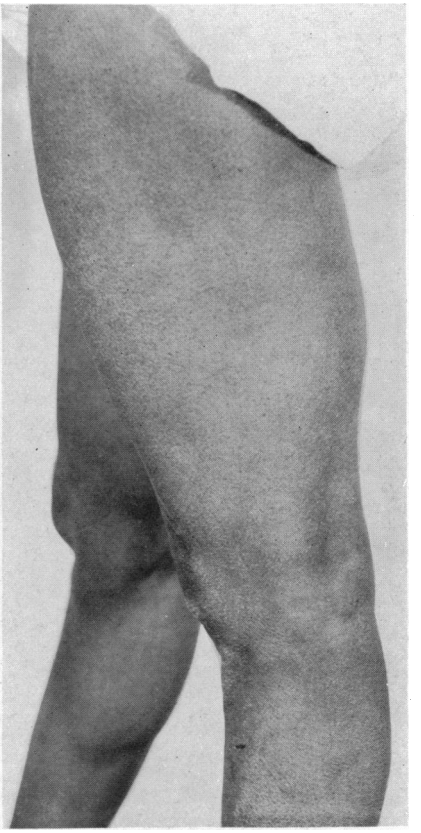

FIG. 6.—The tumor described in FIG. 5 may be seen forming a prominence on the posterior surface of the thigh about the middle.

CASE II.—M. C., colored, female, aged forty-three years, was admitted to the hospital March 29, 1930. She complained of a lump in her left thigh posteriorly about the middle. She also complained of pain which radiated to the knee and into the foot. Her symptoms dated from April, 1922, and began four months after an operation for a "tumor of the stomach" when she accidentally discovered the lump referred to above. The lump has not increased in size since its discovery. Several weeks ago, while in bed, she experienced suddenly sensations of pins and needles in her left foot. This was followed by aching pains in the sole of the foot, big toe and knee. The pains were not increased by standing and walking. They occurred chiefly at night. Some tenderness is noted over the lower pole of the tumor.

On examination a circumscribed, deeply located tumor is found on the posterior side of the left thigh at the junction of the middle and lower thirds. Pressure upon this causes pain to run down the patient's leg over the distribution of the great sciatic nerve. No impairment of the functions of the leg and foot is observed. Sensation is preserved.

April 3, 1928, the tumor was exposed and the sciatic nerve mobilized. An attempt was made to enucleate the tumor, but the fibres of the sciatic nerve were incorporated in it and a resection of the nerve was necessary. An end-to-end suture was performed. The knee had to be flexed at a right angle in order that the nerve suture could be performed. A plaster-of-Paris case was then applied. The leg was gradually extended to its normal position after eight weeks.

The tumor was about the size of a hen's egg. Grossly it had a myxomatous appearance. The funiculi of the nerve were so closely related to the tumor that enucleation was impossible.

This patient was examined July 10, 1930. There has been a marked improvement in function. Plantar flexion is relatively strong. There is some dorsal flexion. The patient walks without the aid of a cane, and although there is some foot drop the toe of the shoe is no longer scraped.

CASE III.—C. D., white male, aged sixty-three years. The patient first noticed a mass in the back of the left thigh three years ago. Two years ago pain, which ran down the left leg into the foot, particularly to the dorsum of the foot at the base of the great toe, was noted. This pain has become decidedly worse and more persistent. It is now constant, but varies in intensity. There is no difficulty in walking, and walking does not make the pain more intense. The left leg seems to be colder than the right. The patient complains considerably of the cold sensation and wears an extra sock to counteract it.

FIG. 7.—Sarcoma of the sciatic nerve. Exceedingly rapid growth. Metastatic nodules have formed along the course of the nerve and extended toward the pelvis. Thigh amputation after attempt to cure by resecting the sciatic nerve.

FIG. 8.—Tumor of the sciatic nerve and its branches. Small nodules may be seen in the branches of the nerve below the site of the original tumor.

A small, ill-defined mass is found in the left buttock near the gluteal crease. This measures about three centimetres in diameter. Another mass is found in the upper part of the popliteal space along the course of the great sciatic nerve. This is not attached to the skin. It is deeply situated, and it is difficult to outline the tumor accurately. Sensation is not interfered with and there is no loss of motor function.

October 10, 1929, the left sciatic nerve was explored under local anæsthesia. The incision was above the site of the tumor, which was not located. A definite localized fatty mass was removed. The symptoms persisted. When the patient was in the right position the mass could be located, and on December 13, 1929, another operation was

performed. This was begun under local anæsthesia, but had to be continued with gas. The tumor was exposed and the internal popliteal nerve mobilized. The tumor was apparently encapsulated. The nerve was split. Most of the tumor could be enucleated. Some funiculi were so closely attached to the capsule that they had to be sacrificed. These funiculi happened to be sensory. The patient has some anæsthesia on the back of the leg.

This tumor resembled the other two in gross appearance. It was myxomatous. Throughout the solid parts of the tumor were small cysts. Scattered throughout the tumor were small yellowish areas.

The three tumors just described are typical of the remaining twelve of the benign group, and the other histories and microscopic findings will not be discussed. They belong to a group of tumors to which Verocay has given the name of neurinoma. These tumors clinically are benign. Some have undoubtedly been classified as sarcomas or fibromyxosarcomas. Because of areas of localized nuclear richness they have been regarded as resembling histologically tumors arising in other tissues which run a malignant course. Verocay first recognized the nature of these tumors and believed that they were composed of tissue which had some relation to the sheath of Schwann. The neurinomatous tissue is of two types. Type A is characterized by a palisade arrangement of the nuclei. The tissue is decidedly polar in arrangement and appears in long bundles or strands. The so-called nuclear rows of Verocay appear only in type A tissue. They are quite characteristic. The nuclear arrangement with polarization reaches its highest expression in neurinomas, and may be considered characteristic of them. This type may be relatively abundant in some tumors; in others there may be but little. In some there may be none of this type. Transitions between types A and B are found, type B having apparently differentiated from type A. There is a tendency for hyaline degeneration to occur in the intercellular substance of the type B tissue. This degeneration occurs in this type only, and sometimes to a high degree. It gives to it the glistening appearance and transparency of connective tissue hyaline. This tissue is, as a rule, softer than that of even a soft fibroma. If smaller or larger masses of the hyaline material fuse and swell, cyst-like structures are formed, which displace neighboring tissue and lead to a thickening of the same, which form a capsule about the tumor. Types A and B occur together in many of these tumors. The transitions between the two may be gradual. In some instances they are sharply demarcated from each other. In other tumors type A tissue occurs in sharply delimited islands scattered throughout the reticular type B tissue. Type B tissue is found in all tumors, while type A is absent relatively often. The whorls and vortices of type A may be preserved in type B, but are made up of a different tissue.

The histological structure of these tumors is well illustrated by the tumors which were removed from the three cases cited.

Fig. 1 is a photograph of a cross-section of the tumor removed from Case I. The capsule of the tumor has been broken at one place. Along the middle of the upper

border of the tumor is an area of solid tissue occurring in islands, some of which are more or less fused. This is type A tissue. The greater part of this tumor is made up of the reticular type B tissue in which changes had occurred, giving rise to the myxomatous appearance of the tumor.

Fig. 2 is a photomicrograph through the tissue at the middle of the upper border of the tumor. The palisade arrangement of the nuclei and the polar arrangement of the fibrils are well shown in this section.

Fig. 3 is a photomicrograph of a section through the tumor of the sciatic nerve described under Case II. Islands of type A tissue with the palisade arrangement of the nuclei may be seen. These are surrounded by type B tissue, in which the changes giving rise to tissue of a myxomatous appearance occur.

Fig. 5 illustrates the vortices and whorls of type A tissue in a tumor removed from the sciatic nerve. The palisade arrangement of the nuclei is well shown in this section. Transformation of this into type B may occur, but when this occurs the whorl and vortices arrangement is preserved.

The same tissue is found in spinal-cord and spinal-nerve tumors. It is also found in dural endotheliomas and acusticus tumors. A palisade arrangement of the nuclei and tissue resembling the type A is found also in some myomas and myosarcomas.

As already stated, Verocay was the first to suggest that these tumors were composed of a tissue which had some relation to the sheath cells, and gave to them the name neurinomas. Penfield has remarked that the term neurinoma—applied to the solitary nerve tumor—has been unfortunately widely accepted. The term conveys a definite meaning and will probably remain in the literature. Although there may continue to be discussion as to the tissue involved, the term conveys a very definite meaning. The presence of this tissue in both solitary tumors and the tumors of von Recklinghausen's disease led Verocay to assume that the tumor develops from the sheath cells. These tumors do not arise from the sheath cell, which is of ectodermal origin, but from connective tissue sheath about the fibrillæ.

Fifteen solitary tumors of peripheral nerves compose this group. Fourteen have been enucleated from the nerve. In one case the sciatic nerve had to be resected. On gross examination they appeared myxomatous. These are benign tumors, as none has recurred. They have a definite histological structure and belong to the neurinoma or perineurial fibroblastoma group. The nearer the periphery the tumor is located, the more the type B tissue predominates over the type A.

Von Recklinghausen's Disease (Neurofibromatosis).—It should be remembered that patients with this disease do not come to the hospital for treatment until the superficial tumors are large enough to cause disability or disfigurement, or until the involvement of deep nerves gives rise to symptoms. A few of the patients under consideration were admitted for other conditions. One patient came to the hospital to have all the skin tumors, numbering 118, removed. The group considered in this paper must be regarded as representing the late rather than the early stages of von Recklinghausen's disease.

There are sixteen cases in this group. The ages range from four to fifty-six years. The small skin tumors and pigmented areas dated from birth

or childhood in the eleven cases in which a note was made as to duration. Frequently the tumors reached a certain size and then ceased to grow. Other tumors continued to appear either as new developments or as the result of growth of minute nodules which had not been discovered previously. The superficial tumors, as a rule, were widely distributed over the trunk, head and extremities. Three of the patients with superficial tumors, without evidence of deep lesions, requested operation because of the size of one or more tumors. One patient entered the hospital for the excision of all the visible nodules. A tumor was removed for histological study from a patient on the

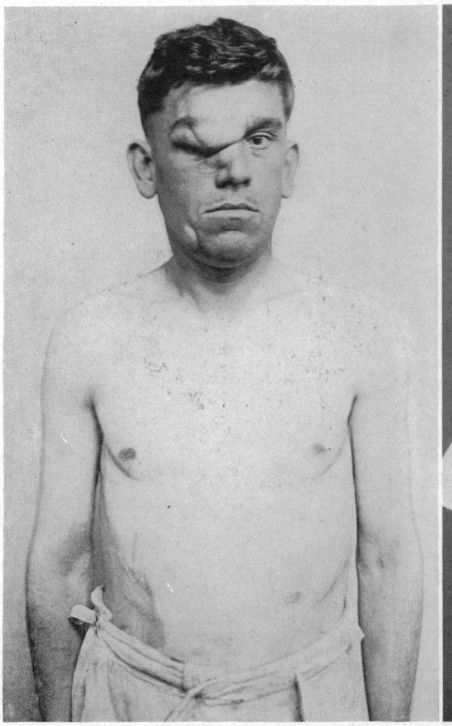

FIG. 9.—Von Recklinghausen's disease with multiple subcutaneous nodules and a lobulated mass over the right eye.

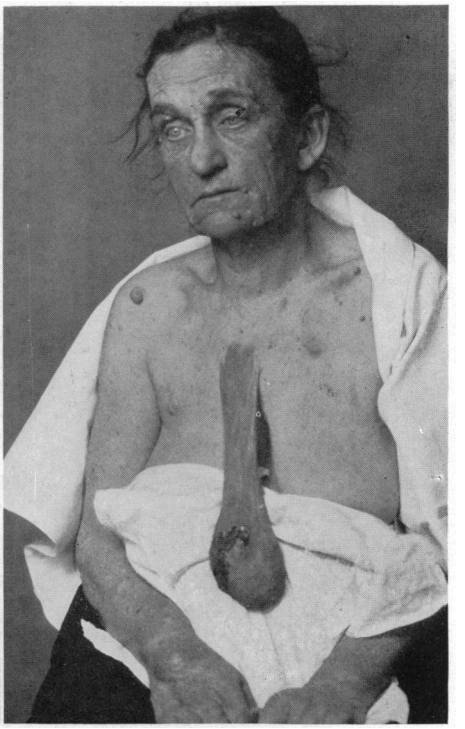

FIG. 10.—Von Recklinghausen's disease. Multiple nodules in the skin with pigmentation of skin and a pendulous tumor of the chest wall.

obstetrical service. In some instances the superficial tumors were scattered indiscriminately over the body. In a number of cases, however, there was a linear arrangement along the superficial nerves, usually a symmetrical distribution. Pigmentation of the skin was mentioned seven times, but it was undoubtedly present in other cases. The areas of pigmentation varied in size from a few to as many as six to eight square millimetres. These areas were scattered irregularly over the body and extremities.

In this group of sixteen cases there were five without and eleven with deep nerve tumors.

The following are examples of neurofibromatosis in which the deeper

nerves are not involved. These cases are not uncommon, and the histories of but three cases will be given.

E. S., colored female, aged twenty-six years, states that she had tumors of the skin as long as she can remember. She has had paræsthesia of the extremities and has been unable to walk since having a hernia repaired several weeks ago under spinal anæsthesia. Pigmentation of the skin is marked. She thinks that more nodules have appeared in the skin over the chest during the past week.

On examination numerous subcutaneous and deeper nodules of varying size, which are soft, freely movable and not tender, are found scattered over the body. The distribution of these nodules does not correspond to nerve distribution. There are pigmented areas upon the back. The patient has mental symptoms and quite severe psychic disturbances. A skin tumor was removed for diagnosis. The diagnosis was neurofibroma (von Recklinghausen's disease).

E. C., white female, aged fifty-six years. This patient has had tumors in the skin of

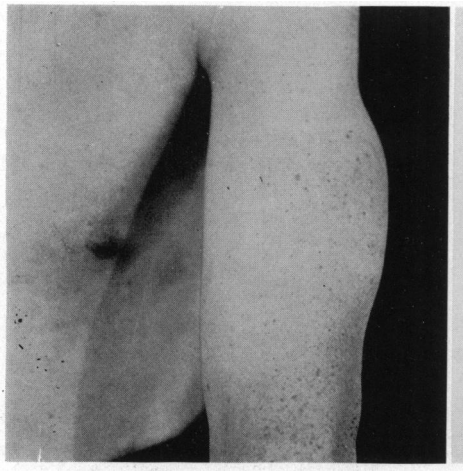

FIG. 11.—Von Recklinghausen's disease with tumors on deep nerves. These have a symmetrical distribution. The prominence on the posterior part of the arm is caused by a tumor on the radial nerve. This tumor was enucleated, the fibres of the nerve remaining intact.

FIG. 12.—Tumor removed from the median nerve of the patient represented in FIG. 11. This tumor was enucleated. It had a myxomatous appearance on cross-section.

the face and chest as long as she can remember. There are also pigmented areas in the skin which are most marked in the skin of the right upper extremity. A pedunculated tumor the size of an orange hangs from the mid-line of the chest down over the abdominal wall. The base of the pedicle is the size of a half dollar. The pedicle is at least six inches in length. The dependent part of the tumor is ulcerated and anæsthetic. Sensation is present over the base of the tumor. The remaining tumors have appeared at various times, although many were present at birth.

April 27, 1926, the large pedunculated tumor, measuring twenty-seven centimetres in length, was removed by Doctor Cohn. A wide margin of skin and subcutaneous fat was removed with the tumor. On section the tumor was firm, hard and fibrous beneath the ulcer. In other parts it was soft and vascular. The microscopic examinations revealed a fibromyxoma with areas so vascular that the possibility of a hæmangioma was considered.

N. W., white male, aged twenty-six years. Seven years before admission to the hospital the patient had had a growth removed from above the right eye. Two months

after removal the tumor developed again. Five years before a growth had been removed from the right foot and from the chest. Since childhood he had noticed numerous soft, painless nodules over the surface of the body. These, with the exception of the large one which was excised, have given him no trouble.

The patient has the typical appearance of von Recklinghausen's disease. Numerous soft tumors lying in or just beneath the skin are found. July 10, 1920, Dr. Mont Reid removed tumors from the forehead and cheek. The diagnosis of pigmented neurofibromas was made.

The three cases cited above are typical of von Recklinghausen's disease. It is interesting to note the pathological diagnosis which has been made, for not infrequently the myxomatous character of the tumor has been emphasized. In one the vessels were prominent enough to suggest a vascular tumor. The superficial group of tumors has developed from cutaneous nerves.

There are eleven cases in which tumors have been found upon the deep nerves. In four of these malignant changes occurred. Malignant changes in tumors situated upon deep nerves are not at all uncommon in these cases. Garrè, in 1890, directed attention to the tendency for such tumors to become malignant.

G. B., white male, aged twenty-eight years. The patient was first admitted to the medical service in August, 1920. He had tumors distributed over the entire body which had been present since early childhood. The tumor behind his right ear was noted by his mother when he was one year old. New tumors have appeared from time to time. These tumors are circumscribed, grow for a time, become stationary, but do not disappear. They are not painful or tender. In 1918 a tumor behind the right ear was excised and a tumor on the left leg was partially removed. The patient was admitted to the hospital again August 8, 1926, when a small tumor on the left side of the chest was removed. Histologically this tumor was like those found in von Recklinghausen's disease. Recently there has been some stiffness of the left knee and disturbance of function of the left leg. These are due to a large pedunculated tumor which has been present for fifteen years, but recently has grown larger and now hangs down over the knee. Numerous small tumors are scattered over the body. A large boggy tumor mass is found on the anterior aspect of the left thigh which extends from a little below Poupart's ligament to below the knee. The overlying skin is soft and elastic. Palpation of the tumor suggests a fluid wave. The patella is located in this mass of tissue.

October 4, 1926, at operation a large cavity was found in the tumor which communicated with the joint. When this was opened about 800 cubic centimetres of fluid were evacuated. A specimen was taken for examination. The tumor seemed to infiltrate the muscle and was not removed. The patient returned to the hospital again in January, 1929. A large mass had developed in the left half of the pelvis just above Poupart's ligament. On examination a large, hard mass is found in the pelvis and the left lower quadrant of the abdomen. This extends from Poupart's ligament to the umbilicus and causes the abdominal wall to protrude. This tumor is firmly fixed, rises from the pelvis and extends over to the mid-line. The tumor of the left thigh is much smaller than when the patient was here before. January 19, 1929, a biopsy was performed. Part of the tumor was excised without opening the peritoneal cavity. This tumor was firm and fibrous in character.

A diagnosis of spindle-cell sarcoma was made. The patient has been receiving radium treatments. When seen in Baltimore several months after the biopsy the tumor was of about the same size as when the tissue was removed.

E. H., white female, aged fifty years. This patient was operated upon December 1, 1922. Since childhood she had complained of a drawing pain in the left leg and thigh.

She had worn red flannels to relieve this. The leg has been massaged for relief of this pain. Curious pigmented spots and blotches are found over the abdomen and extremities. Since childhood numerous painless, somewhat firm, subcutaneous nodules have been noted over the body. These have increased but slightly in size, and at the present time measure from two to six millimetres in diameter. The pains in her left leg have been more severe during the last ten years. About six years ago she noted that her left hip seemed slightly larger than her right. For the last year she has noticed a definite growth. This tumor was operated upon one year before admission to the hospital and found to be attached to the sciatic nerve. It could not be entirely removed. Since that time it has grown rapidly in spite of radium treatment. The pain has been so severe that narcotics have been required. Hearing in the right ear is

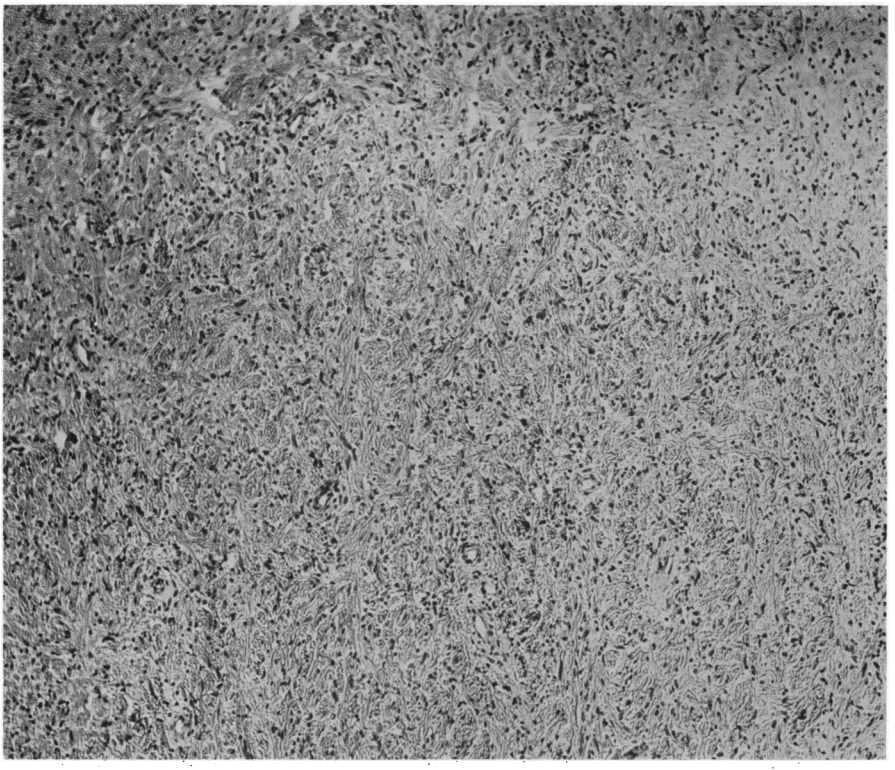

FIG. 13.—Histological preparation of the tumor shown in FIG. 12. This tumor is mixed, containing bands of fibrous tissue. Scattered between these are islands of reticular tissue (type B). These tumors have a decided tendency to undergo malignant (sarcomatous) changes.

impaired and at times the patient complains of numbness of the right side of the face. The patient has evidently lost weight recently. The tumor on the left thigh is about the size of a football, measuring twenty-four by eighteen centimetres. Over this is a scar twenty centimetres long. There is no muscular weakness in the left leg. The skin over the body has a mottled appearance. The pigmented areas, varying in size from a pinhead to a silver dollar, are irregularly distributed. The possibility of a tumor on the eighth nerve was considered because of the impairment of hearing.

December 1, 1922, the tumor in the thigh was removed. It apparently rose from the great sciatic nerve. Only a partial removal was possible. When the tumor was cut across it had a lobulated, yellowish, pearl-gray appearance. The patient was a poor operative risk and died a few hours after the operation.

Pathological diagnosis.—Spindle-cell sarcoma with extensive necrosis and degeneration. Malignant degeneration of a tumor in von Recklinghausen's disease.

The following are cases of von Recklinghausen's disease with tumors of deep nerves without malignant changes. The specimens which were removed illustrate especially well the histology of these growths and how they differ from that of the solitary tumor.

E. R., white male, aged twenty-one years, was admitted to the Johns Hopkins Hospital October 10, 1927. The patient has small tumors scattered over the body, most of which correspond to the course of superficial nerves. He came to the hospital especially because of symptoms associated with a tumor over the course of the left musculospiral nerve, located where the nerve is in the radial groove. Numerous well-circumscribed tumors of various sizes, from a small shot up to a small orange, are scattered over the body. The greater number of nodules are about the size of a pecan. Practically all are superficial, firm and rubbery in consistency, and, in general, follow the course of superficial nerves. In the left arm along the course of the radial nerve in the radial groove is a fusiform tumor, constricted at the middle. Pressure on this causes a tingling sensation over the distribution of the radial nerve. Pigmented areas are scattered over the body.

At operation, October 10, 1927, a tumor was found upon the radial nerve. The tumor was removed by splitting the nerve, the fibres of which seemed to form a capsule about it. The tumor was shelled out of the nerve. The pathological diagnosis was neurofibroma. The patient returned in March, 1930, with a large tumor on the median nerve of the right side just below the axilla. This tumor was removed by separating the fibres of the nerve and shelling it out. This tumor was more myxomatous in character than the tumor previously removed from the musculospiral nerve. Neither tumor has recurred. It should be remembered, however, but a short time has elapsed since their removal.

The following cases, which might be included under the term Ranken neurom, have been characterized by multiple growths upon the nerves of an extremity associated with an increase in size of all the tissues of the extremity.

R. R. is a female child, aged four years. About sixteen months before operation, September 28, 1928, a general eruption resembling insect bites appeared upon the body. This eruption appeared from time to time. It was noticed then that the left leg and thigh were larger than the right. The enlargement involved the leg, thigh and half of the pelvis on the left side. Thirteen months before admission small, tender, subcutaneous nodules appeared about the upper end of the fibula. The child has not complained of pain, but she favors the right leg somewhat. The nodules have increased somewhat in size. The left lower extremity is distinctly larger than the right and has none of the changes associated with a lymphœdema. The hypertrophy involves all the tissues from the gluteal muscles to the tips of the toes. Muscle power is not reduced. There is no limitation of motion, no spasticity nor pain. There is some eversion of the left foot. Near the left knee and ankle both medially and laterally there are firm, discrete masses which have a linear distribution and are apparently connected with nerves. These are especially well marked posterior to the medial malleolus. All the other parts of the body are normal.

Some of the nodules along the posterior tibial nerve were removed for study. A pathological diagnosis of neurofibroma was made.

The following case has been reported by Dr. Willis Campbell:

A. E., a white child, aged fourteen years, has the following history. When the patient was one and a half years old the mother noted that the right ankle and foot were larger than the left. Shortly after that it was noted that the entire extremity was larger. This relative difference in size has been maintained. Examination shows a healthy girl of fourteen with no abnormality except in the right lower extremity. This extremity is enlarged, being increased in length and circumference. Deformity at both the knee- and ankle-joints is noted. The patient walks with difficulty as the weight is transmitted onto the dorsum of a club-foot. The extremity has many diffuse, lobulated

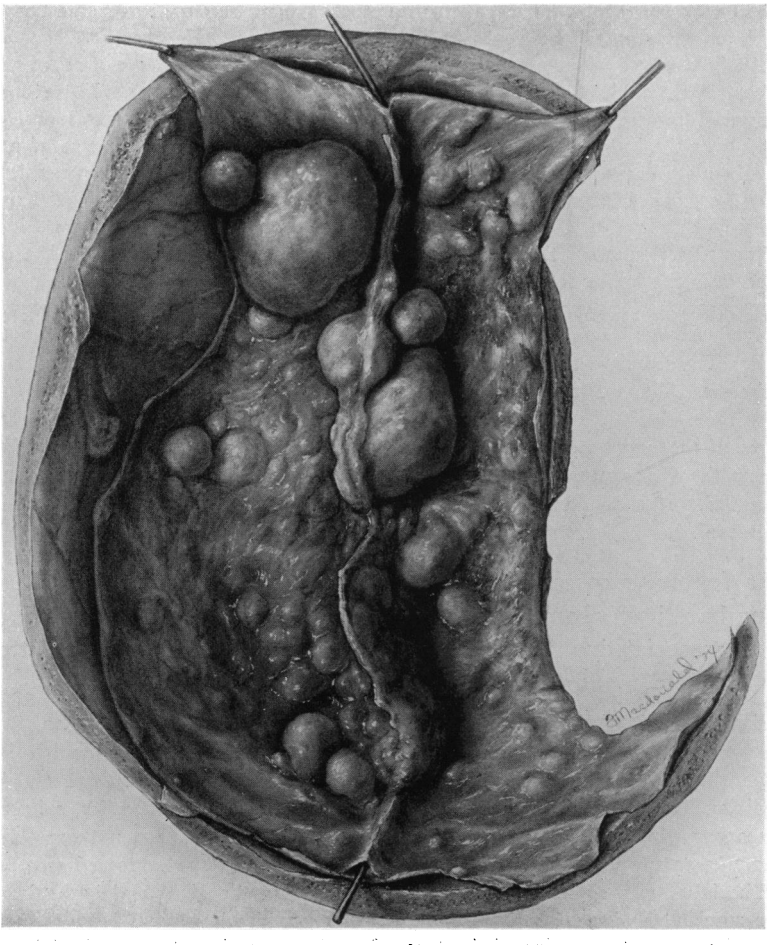

FIG. 14.—Von Recklinghausen's disease. Multiple tumors arising from the dura (Dandy).

tumors beneath the deep fascia which are differentiated with difficulty from the muscles. These cylindrical masses are from one to two inches in diameter. These masses are tender. Measurements show that the right thigh is four inches larger than the left, and the right calf three inches larger than the left. The right lower extremity is five and a half inches longer than the left. Muscle power in the right leg is not impaired. X-ray of the right lower extremity shows that the bones are increased in length, decreased in diameter and atrophic.

Doctor Campbell, by repeated operations, removed numerous lobulated tumors. The

leg was considerably diminished in size. The femur was shortened and the ankle stabilized by removing the astragalus. The lower epiphysis of the tibia and fibula were destroyed, as it was thought that abnormal growth from other parts would counterbalance the effect of epiphyseal destruction. After four operations on the soft parts and two on the skeleton the extremities were of equal length, but the right leg was greater in diameter than the left by one inch.

The pathological report is as follows: The section shows loose tissue composed of strands with few nuclei. There is much homogeneous material which resembles coagulated lymph between the cells. One pathologist reported that he identified nerves in the growth.

These six cases represent different clinical manifestations of the same disease: the cutaneous form of von Recklinghausen's disease, a form associated with tumors upon the deep nerves in which there is a decided tendency for sarcomatous degeneration of the tumor, and a form localized to an extremity which becomes enlarged and to which the term of elephantiasis nervorum might properly be applied, although this term has been applied to other lesions of this type other than the two last described.

Elephantiasis Nervorum.—Bruns, in 1891, published an article upon Rankenneurom in which he states that this tumor is one of the rarest and most peculiar. Two of the first cases were observed by Depaul, in 1857, and Guersant, in 1859. These were carefully studied by Verneuil. Two were reported by Billroth, in 1863 and 1869. Bruns states that the greatest interest attaches to the origin of these tumors and their relation to other nerve tumors. According to him this is a form of congenital elephantiasis; if by this term is understood a congenital anlage leading to tumor-like connective-tissue growths which may affect skin and subcutaneous tissues, sometimes the blood-vessels, the lymphatic vessels and nerves (elephantiasis telangiectodes, lymphangiectodes, neuromatodes). Bruns grouped under the term elephantiasis nervorum—generalized neurofibromatosis—the cases in which the tumor involved a limited area of distribution of the nerve (Rankenneurom), and those cases in which the changes involved the ends of the cutaneous nerve (fibromata mollusca). The localized forms differ in extent, not in nature, from the generalized.

Garrè has pointed out the tendency of tumors in neurofibromatosis to become malignant. Malignant degeneration occurs in at least 12 per cent. In the cases reported by us, although the series is too small to permit of definite conclusions, malignant degeneration has occurred in 50 per cent. There are many transitions between the benign and malignant growth, so that it is difficult to determine at times where benignancy ends and malignancy begins. In Garrè's case ciliated epithelium was found, suggesting a teratoma. This brings up the question of possible development of these cells from the sheath of Schwann. Cohn has reported epithelial tumors in peripheral nerves which probably have developed from the sheath cell.

Trauma and operative interference may predispose to malignant changes, and the possibility of such a change occurring after partial removal of one of these growths should always be considered. This group of connective tissue

growths differs from the group of benign tumors first described, in which there is little, if any, tendency to malignant changes. Virchow recognized the tumors occurring in von Recklinghausen's disease as due to an overgrowth of connective tissue. Wood, Smith and von Recklinghausen also recognized the connective tissue origin of these tumors. Penfield states that a pure neuromfibroma in one sense is not a neoplasm at all. There are wandering nerve fibres derived from the involved nerve and a surrounding tangle of reactionary connective tissue which is a magnification of the widespread alteration of the nerves in this systemic disease. Confusion arises from the fact that at times within these neurofibromata, perineurial fibroblastomata may appear and may grow so large as to displace most of the neurofibroma tissue to the periphery. In the case of von Recklinghausen's disease, however, nerve fibres will be found to enter each tumor, with few exceptions; while in the solitary perineurial fibroblasto-

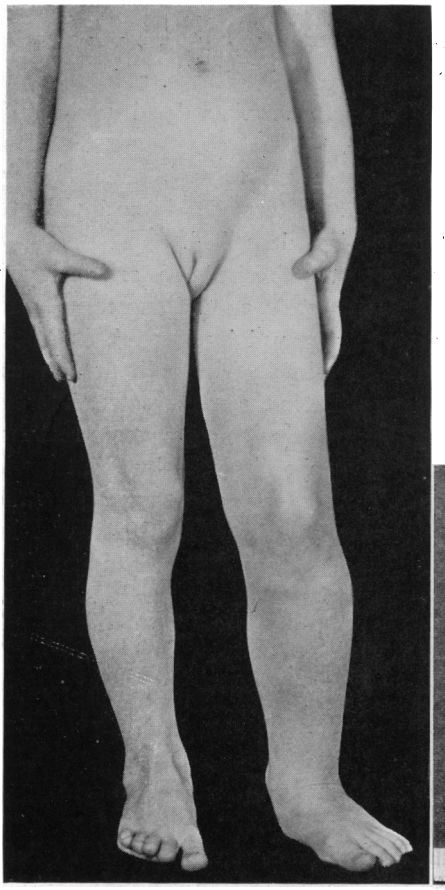

FIG. 15.—Elephantiasis nervorum. The left lower extremity is enlarged. Multiple nodules can be palpated over the nerves. These are especially marked over the short saphenous nerve.

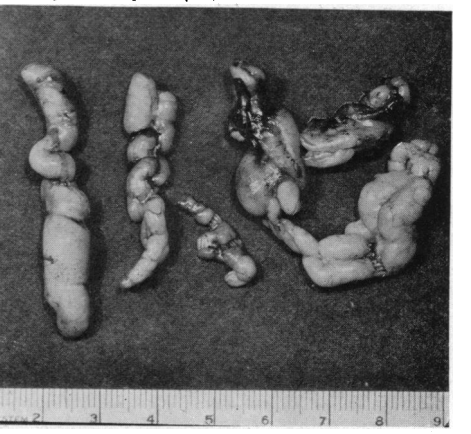

FIG. 16.—These tumors were removed from the posterior tibial nerve just behind the internal malleolus in patient represented in Fig. 15.

mata, the comparatively normal nerve is invariably applied to the capsule of the tumor without penetrating it.

This last statement is undoubtedly subject to exceptions, for, if it were so, all neurinomas could be enucleated. In one of our cases, a typical neurinoma, resection of the sciatic nerve was necessary because the tumor was penetrated by funiculi, and in another some fibres of the internal popliteal had to be sacrificed.

In the neurofibromas of von Recklinghausen's disease the tissue is mixed. This can be seen readily in studying sections. Many of the tumors may be pure fibromas. In the multiple neurofibromas the neurinomatous tissue is the loose, delicate, reticular type (type B). The centrally located tumors occurring in von Recklinghausen's disease may be composed entirely of neurinomatous tissue. This accounts for the relative frequency with which central degenerative changes occur in these.

The solitary tumor and the multiple tumor of von Recklinghausen's disease differ histologically. Clinically, we are justified in concluding that there is a great difference as regards the possibility of malignancy between the solitary tumor and the multiple tumor of neurofibromatosis. There is also a great difference in the histology. A peripheral nerve is a complicated structure composed of highly differentiated epithelial and connective tissue elements, which in their growth may give rise to specific and characteristic structures. The sheath of Schwann may, in tumor formation, give rise to a growth distinctly epithelial in character. This change probably accounts for the epithelial tumors in peripheral nerves recently reported by Cohn, and the ciliated epithelium observed by Garrè in a malignant tumor occurring in von Recklinghausen's disease.

Sarcomas.—In this group are four tumors. The histories of these will be given. Two illustrate the mode of extension of a sarcoma, and one the possibility of at least a long period of freedom from recurrence following operation.

T. M., white male, aged fifteen years, noticed pain December 15, 1928, just above the knee along the hamstring muscles. A tumor about the diameter of a twenty-five-cent piece appeared later in the region where the pain was first experienced. The tumor was aspirated but nothing was obtained. An operation, the nature of which cannot be ascertained, was performed March 14, 1929. The patient remained in the hospital two weeks. Since then the patient has complained of numbness of the leg. An examination made upon June 7, 1929, showed that the right leg was flexed at the knee. A long scar is noted on the posterior surface of the thigh. The right thigh is larger than the left, and in the region of the scar over the posterior part of the right thigh is a movable mass. It is impossible to say whether this is the original tumor or a recurrence. An X-ray examination revealed a large, soft-part tumor which extended along the course of the sciatic nerve well up into the gluteal region. There were no evidences of metastases in the chest.

Doctor Bloodgood believed that the tumor developed from the sciatic nerve and that an amputation of the thigh should be performed.

The tumor was adherent to the muscles, quite myxomatous and œdematous. Small tumors were found on the branches of the sciatic nerve. Some of the tumor mass extended beyond the sciatic notch, rendering complete removal impossible.

The branches of the sciatic nerve below the popliteal space were covered with white, smooth, myxomatous masses. The large, and probably the original, tumor has many necrotic, hæmorrhagic areas. The pathological diagnosis was fibromyxosarcoma of the sciatic nerve.

The second case illustrates again the tendency of a sarcoma to extend along the nerve.

M. M., white male, aged forty-one years, noted in 1910 a hard nodule in the lower lip. This did not ulcerate. It was enucleated. Since this first enucleation the tumor

has recurred and has been removed fifteen times. The last operation was performed in June, 1915. No ulcer had formed. The cervical lymph nodes had not been removed. X-ray treatments had been given at various times for five years.

A histological study of the tissues which had been removed at previous operations revealed a cellular tumor composed of spindle and round cells. In some sections nerve tissue was found in the tumor. The tumor was thought to be multiple neurofibroma.

September 10, 1915, Doctor Bloodgood removed the lower jaw and submaxillary glands. The inferior dental was as large as a thumb. The tumor extended up to the point at which the nerve emerges from the skull. This point was cauterized. Histological examination revealed much the same picture as that of the tissue previously removed. The cells were, however, larger and more irregular in size.

The patient died January 26, 1916, with cerebral symptoms, apparently due to an

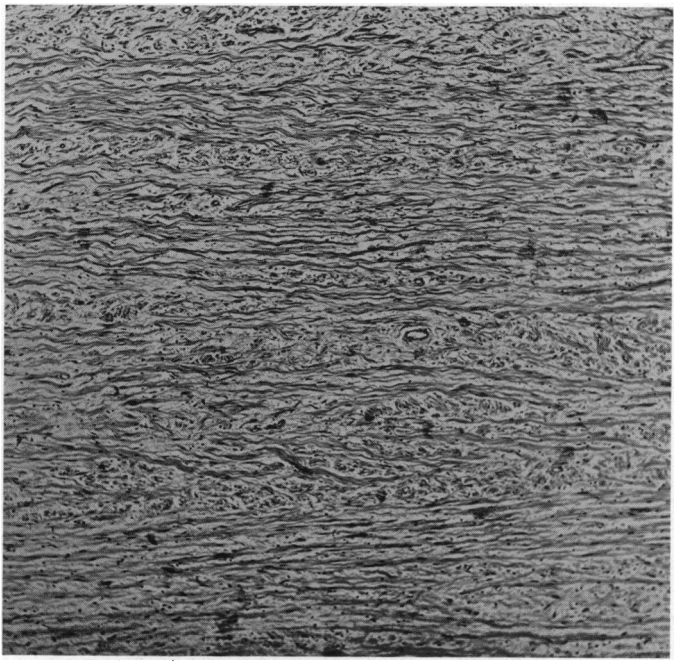

FIG. 17.—Histological preparation of the tumors shown in Fig. 16. The histology differs markedly from that of the solitary tumor (neurinoma) of peripheral nerves.

extension of the growth to the cranial cavity. This tumor, regarded at one time as a multiple neurofibroma, was undoubtedly malignant, as indicated by the number of recurrences in the lip and final extension to the skull.

A third sarcoma involved the internal popliteal nerve on the left side. The nerve was resected. Seven months after operation there was a recurrence, and a little over five years after the first operation the patient died. A diagnosis of round-cell sarcoma was made.

Dr. Miles F. Porter has kindly furnished us with the history of a case in which a tumor developed in the upper third of the thigh posteriorly in a female patient aged fifty-two years. This tumor caused pain which radiated down to the ankle and up to the hip. A tumor was removed in August, 1923. Six months later another tumor was removed. This was situated a few inches above the original tumor. Seven months later the tumor recurred and was removed again. During one and three-quarter years this tumor recurred frequently.

On July 2, 1923, Doctor Porter operated and removed an encapsulated tumor the size of a small orange from the muscles on the posterior surface of the thigh. A diagnosis of sarcoma was made from frozen sections. The bed of the tumor was cauterized (actual cautery) and alcohol applied to the wound surface.

Subsequently, after many recurrences the sciatic nerve with a tumor was resected and a fascial tubulization performed. Five years later the patient reported that there had been no recurrence of the tumor. Some foot drop persisted and there were sensory changes associated with resection of the sciatic nerve. It is impossible to determine the origin of this tumor, but eventually it involved the sciatic nerve, necessitating its resection. It may have arisen primarily in one of the branches of the sciatic, and secondarily have invaded the main trunk.

Sarcomas of peripheral nerves, as already stated, are extremely malignant and tend to form metastases along the nerve primarily involved. They may, however, extend to other nerves in the extremity, passing to these apparently along branches communicating with the nerves primarily involved.

Two rather unusual tumors were encountered in this series, one arising apparently from the cervical sympathetic, the other from the vagus.

Tumor of the Cervical Sympathetic.—G. N., white male, aged forty-one years, had a small mass on the left side, about the middle of the neck, for eighteen years. At first this was about the size of a cherry. It gradually increased in size, but it has not increased in size any more rapidly of late. There has been no pain. There has been no difficulty in swallowing until recently, when there is a slight sensation of pressure on swallowing and occasionally on breathing.

Examination reveals a tumor on the left side of the neck. It is elliptical and fills practically the entire space between the angle of the jaw and the clavicle. It has displaced the trachea and the carotid artery to the right side. The carotid artery has been displaced so far forward and to the right that it can be seen beating almost in the midline of the neck. There is no difference in the pupils on either side. They react normally to light and accommodation.

This tumor could be easily removed. The carotid artery was in front and median to the tumor, the jugular vein and the vagus nerve were in front and to the outside. The most probable origin of this tumor seemed to be the cervical sympathetic trunk. The tumor had little vascular supply and was easily separated from the surrounding structures. The histology of this tumor is represented in Fig. 19. As will be seen, the tumor contains a large number of ganglion cells.

Tumor of the Right Vagus Nerve.—The other tumor in this group arose from the right vagus nerve. Because of the pigmented areas in the skin it is quite possible that this tumor belongs to the von Recklinghausen group. There were no other palpable tumors in this case.

The patient, a white male, was nineteen years old. Five years ago he noticed for the first time a small mass behind the right mandible. This caused no pain. Four years ago the mass became larger, and a doctor advised that the tonsils be removed. Later a diagnosis of tuberculous glands was made.

Examination reveals a mass on the right side of the neck. It fills the space between the angle of the jaw and the mastoid, and occupies the upper half of the neck posteriorly. The tumor is the size of a man's fist. The skin over it is freely movable. The surface of the tumor is smooth, with no signs of lobulation. It is sharply delimited from the other structures in the neck. The common carotid artery is anterior to the tumor. The trachea is displaced to the left. There are no pupillary changes which would suggest connection with the cervical sympathetic.

The tumor is apparently fixed by neighboring structures. Von Recklinghausen's disease, a brachial cyst, and carotid body tumor were considered in the differential

diagnosis. This tumor when removed was found to be a fibromyxoma of the vagus nerve. Following removal of the tumor the patient was unable to swallow anything but soft foods and liquids. He strangled when he attempted to swallow. The symptoms which he complained of following operation were due to loss of function of the right superior and recurrent laryngeal nerves.

This case, in view of the marked pigmentation, should probably be regarded as an example of von Recklinghausen's disease. The only palpable tumor developed upon the right vagus nerve. The patient with the tumor of the cervical sympathetic died one year and four months after operation. There was a local recurrence and pulmonary metastases. It has been impossible to trace the patient with the tumor of the vagus. He returned to the hospital six months after having been discharged, and to that time the signs and symptoms associated with paralysis of the vagus persisted.

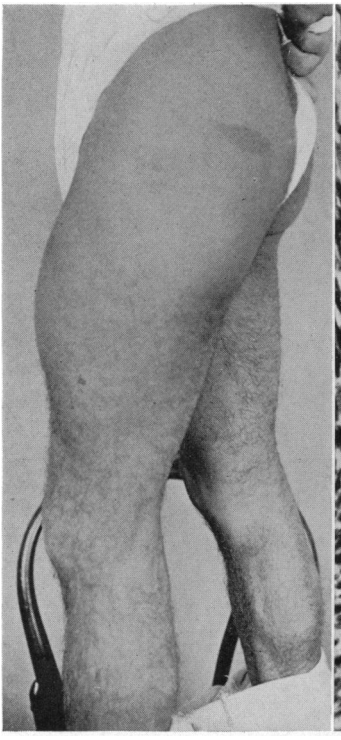

FIG. 18A.—Tumor on the sciatic nerve in a case of von Recklinghausen's disease.

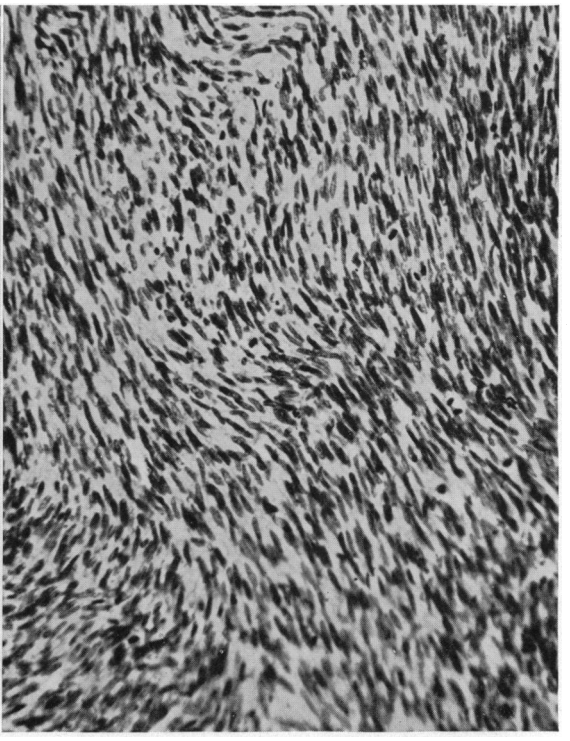

FIG. 18B.—Histological preparation of a recurrent tumor in the patient shown in Fig. 18A. Malignant change in a tumor of von Recklinghausen's disease.

Neurofibromatosis Confined to the Skin, Localized in Extent (Fibroma Molluscum).—R. L., white male, aged twenty years, was operated upon April 10, 1907. The patient stated that since birth a small tumor had been present on the internal surface of the right foot just below the malleolus. This has gradually increased in size, and other tumors have appeared on the internal portion of the plantar surface of the foot. When the patient was thirteen years old the tumors were excised, but in about six weeks others developed. These have increased in number and size until at the present time the entire internal part of the plantar surface of the right foot and great toe are covered with tumors.

On the inner side of the sole of the right foot and great toe are peculiar pedunculated, soft tumors which are more or less separated from each other. They, however, lie side by side and seem to be almost continuous. They are flattened out by the pres-

sure exerted when the patient is standing. In gross appearance they look very much like fibromata mollusca but do not seem to follow the distribution of any one nerve.

On April 10, 1907, the tumors on the inner side of the plantar surface of the foot were excised, as little skin of the pedicle as possible being removed. The skin was brought together, with interrupted sutures of fine silk except in two places, which were allowed to granulate. Eleven years after this the patient reported that there had been no recurrence of these tumors.

The clinical manifestations of different varieties of peripheral nerve tumors have been discussed. An attempt will be made to correlate clinical manifestations and prognosis with histological findings. A peripheral nerve has a complicated structure, being composed of neurofibrillæ, the myelin sheath, the sheath of Schwann and connective tissues surrounding the fibres, funiculi, and nerve. Judging from a study of the tumors in this series and from cases which have been reported, the neurofibrillæ take no part in tumor formation.

Fifteen solitary tumors of peripheral nerves have been described. These have not recurred following operation, and in all but one case the tumor could be enucleated. In one case a large tumor of the sciatic nerve was found. This could not be enucleated because the nerve fibres ran through it. Almost two years after resection and suture there has been no recurrence of the tumor.

These tumors are composed of the neurinomatous tissue described by Verocay. They contain islands or whorls of type A tissue, which is characterized by nuclear palisades. They resemble histologically the acusticus tumor and the tumors developing upon spinal nerve roots, most frequently upon the posterior roots. Degenerative changes, occurring most often in the reticular tissue, may cause the myxomatous appearance of the tumor which is so common.

Lhermitte and others have recently suggested that these tumors characterized by palisading of the nuclei developed from the sheath of Schwann cells, the lemmocyte, and classified them as gliomata. Verocay was the first to suggest such an origin. Penfield states that the fibres produced in these neoplasms show that the type cell bears no relation to neuroglia nor to the ectodermal sheath of Schwann. The histological picture is characterized by palisading and parallelism of the nuclei and a tendency to form nuclear eddies and streams. The fibres are typically long, slender, wire-like, and arranged parallel to each other. These fibres resemble the connective tissue seen in normal nerves where they run parallel to nerve fibres. The term perineurial fibroblastoma has been given to these tumors by Mallory. Clinically thy are benign tumors which, as a rule, can be enucleated from the nerve, leaving the greater part of it intact.

The tumors occurring in von Recklinghausen's disease were described by Verocay as mixed. They were shown by him to be composed of neurinomatous tissue and connective tissue. The nearer the periphery the tumor is located, the more the fibrous tissue predominates. The tumors occurring in von Recklinghausen's disease frequently undergo secondary changes. Such

changes are indicated in the tumor represented in Fig. 18B. This tumor had a decidedly myxomatous character. These tumors are apt to undergo sarcomatous changes. This tendency has been frequently noted, and in the series herein reported, though small, malignant changes occurred in 50 per cent. of the cases. Penfield states that in retaining for the tumors of von Recklinghausen's disease the time-honored name of neurofibroma, the term must be understood to signify a tumor which contains both nerve fibres and connective tissue. It is not a new growth of nervous tissue, although there are nerve fibres and apparently new nerve collaterals running in it. It is not

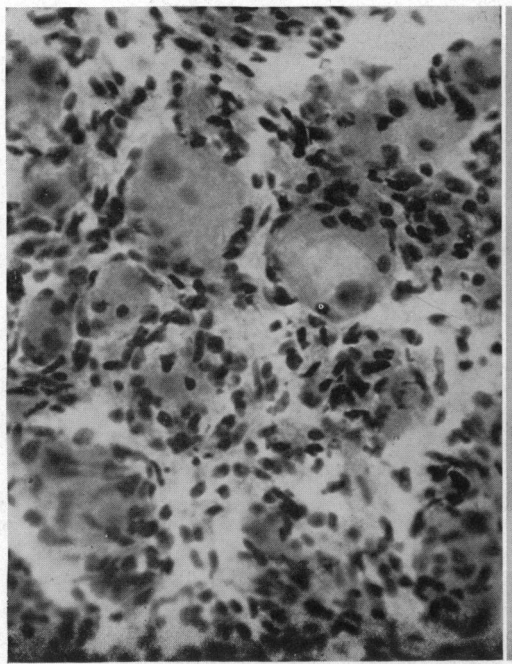

FIG. 19.—Histological preparation of tumor developing from the cervical sympathetic, containing ganglion cells. This tumor was malignant. It recurred locally within a few months after removal, and formed metastatic growths in the lungs.

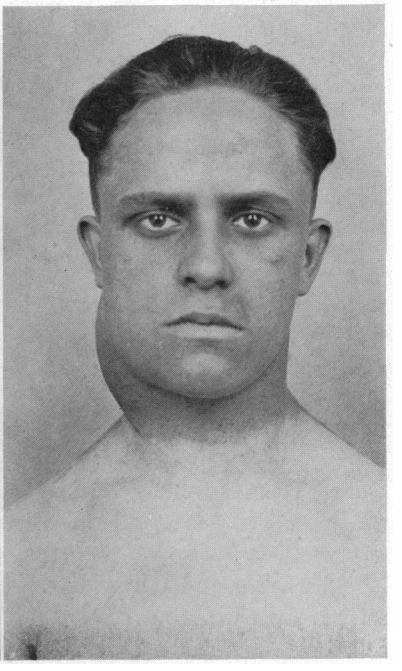

FIG. 20.—Neurofibroma of the right vagus nerve. Diagnosis of this tumor was suggested by pigmentation of the skin. No other tumors palpable on deep nerves. Paralysis of fibres of the vagus followed removal of the tumor.

a simple fibroma but a connective tissue reaction that is part of a more general process.

In the tumors situated peripherally the neurinomatous or fibroblastomatous tissue may be suppressed by an overgrowth of fibrous tissue, a fibroma then being found. Whether the masses occurring upon the nerves in von Recklinghausen's disease should be regarded as tumors or merely as a connective tissue reaction to an irritant may be a disputed question. Clinically, they appear as tumors with a decided tendency to undergo sarcomatous changes.

These growths may be confined to the nerves of an extremity. All the tissues of such an extremity may be affected, resulting in a decided increase

in length and circumference unaccompanied by pigmentation of the skin or any appearance suggestive of a lobulated elephantiasis.

The one case of a tumor developing from the cervical sympathetic is of interest because of the relatively early recurrence of the tumor and the formation of metastases to the lung.

BIBLIOGRAPHY

Antoni, N.: Ueber Rückenmarkstumoren und Neurofibrome. Stockholm, 1920.

Bruns, P.: Ueber das Rankenneurom. Beitr. z. klin. Chir., vol. viii, p. 1, 1891–1892.

Cohn, I.: Epithelial Neoplasms of Peripheral and Cranial Nerves. Arch. Surg., vol. xvii, p. 117, 1928.

Garrè, C.: Ueber sekundär maligne Neurome. Beitr. z. klin. Chir., vol. ix, p. 465, 1892.

Penfield, W.: The Encapsulated Tumors of the Nervous System. Surg., Gynec., and Obstet., vol. xlv, p. 178, 1927.

Roussy, G., Lhermitte, J., and Cornil, L.: Essai de classification des tumeurs cérébrales. Ann. d'anat. path. méd.-chir., Paris, vol. i, p. 333, 1924.

Smith, R. W.: A Treatise on the Pathology, Diagnosis and Treatment of Neuroma. Dublin, 1849.

Thomson, A.: On Neuroma and Neuro-Fibromatosis. Edinburgh, 1900.

Verocay, J.: Multiple Geschwülste als Systemerkrankung am nervösen Apparate. Festschrift f. Chiari, p. 378, Vienna, 1908.

Idem: Zur Kenntnis der "Neurofibrome." Beitr. z. path. Anat., vol. xlviii, p. 1, 1910.

Virchow, R.: Die Krankhaften Geschwülste, vol. iii, p. 233, Berlin, 1863.

Von Recklinghausen, F.: Ueber die multiplen Fibrome der Haut und ihre Beziehung zu den multiplen Neuromen. Berlin, 1882.

Wood, W.: Painful Subcutaneous Tubercle. Med.-Chir. Trans., Edinburgh, vol. iii (part 2), pp. 317, 640, 1829.

Idem: Observations on Neuroma. Med.-Chir. Trans., Edinburgh, vol. iii (part 2), p. 367, 1829.